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DEVELOPMENT, CHARACTERIZATION AND SOLUBILITY STUDY OF SOLID DISPERSIONS OF AZITHROMYCIN DIHYDRATE BY SOLVENT EVAPORATION METHOD

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ABSTRACT

Azithromycin Dihydrate (Poorly water soluble drug), when prepared as solid dispersion showed improved solubility and dissolution. So the main purpose of this investigation was to increase the solubility and dissolution rate of Azithromycin Dihydrate by the preparation of its solid dispersion with urea using solvent evaporation method. Physical mixtures and solid dispersions of Azithromycin Dihydrate were prepared by using urea as water-soluble carrier in various proportions (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 by weight), by employing solvent evaporation method. The drug release profile was studied and it was found that the dissolution rate and the dissolution parameters of the drug from the physical mixture as well as solid dispersion were higher than those of the intact drug. FT- IR spectra revealed no chemical incompatibility between drug and urea. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC) and Powder X-Ray Diffraction (PXRD).

Keywords: Azithromycin Dihydrate; Urea; Solvent Evaporation Method; Solid dispersion.

INTRODUCTION

Azithromycin Dihydrate ((2R, 3 S, 4 R, 5 R, 8 R, 10 R, 11 R, 12 S, 13 S, 14 R)-13-[(2, 6-di deoxy-3-C methyl-3-O-methyl-a-L-ribo-hexopyranosyl) oxy]-2-ethyl-3, 4, 10-trihydroxy-3, 5, 6, 8, 10, 12, 14-heptamethyl-11-[[3, 4, 6, -trideoxy-3(dimethylamino)-β-D-xylo hexopyranosyl]oxy]-1-oxa-6 azacyclopentadecan-15-one) (Figure 1) a macrolide antibiotic of the azalide subclass, exerts its antibacterial action by binding to the 50s ribosomal subunits of susceptible bacteria and suppressing protein synthesis; however, it differs chemically from erythromycin

in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}•2H_2O$ and a molecular weight of 785.0. It is used orally for the treatment of bronchitis, certain types of skin infections, sore throat (pharyngitis, tonsillitis), and pneumonia. One of the major problems with this drug is its very poor solubility in biological fluids that results into poor bioavailability after oral administration. It shows erratic dissolution problem in gastric and intestinal fluid due to its poor water solubility. Rate of absorption and/or extent of bioavailability for such insoluble drugs are controlled by rate of dissolution in gastrointestinal fluids [1]. The peak plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) depend upon extent and rate of dissolution of drug respectively. The effort to improve the dissolution and solubility of a poorly water-soluble drug remains one of the most challenging tasks in drug development. Several methods have been introduced to overcome this problem like solid dispersions, complexation, Zydis technology, and by the use of hydrophilic carriers.

Solid dispersion, which was introduced in the early 1970's [2], refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [2]. Solid dispersion technique has been used for a wide variety of poorly soluble drugs such as nimesulide [3], ketoprofen (4), tenoxicam (5), nifedipine [6], nimodipine [7], ursodeoxycholic acid [8], and albendazole [9]. Various hydrophilic carriers, such as polyethylene glycols [10], polyvinylpyrrolidone [11], hydroxypropyl methylcellulose [12], gums [6], sugar [13], mannitol [14], and urea [8], have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs.

Solid dispersion can be prepared by various methods such as solvent evaporation and melting method. Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug. According to this method, a drug is thoroughly dispersed in a water-soluble carrier by suitable method of preparation. The mechanism by which the solubility and the dissolution rate of the drug are increased includes: reduction of the particle size of drug to submicron size or to molecular size in the case where solid solution is obtained. The particle size reduction generally increases the rate of

dissolution; secondly, the drug is changed from amorphous to crystalline form, the high energetic state which is highly soluble; finally, the wettability of the drug particle is improved by the hydrophilic carrier. Azithromycin Dihydrate-urea systems, prepared by solvent evaporation method, showed an improvement in dissolution rates of the drug from the solid dispersions as compared with the pure drug and physical mixtures. This study presents formulation of solid dispersions of Azithromycin Dihydrate with urea as the hydrophilic carrier.

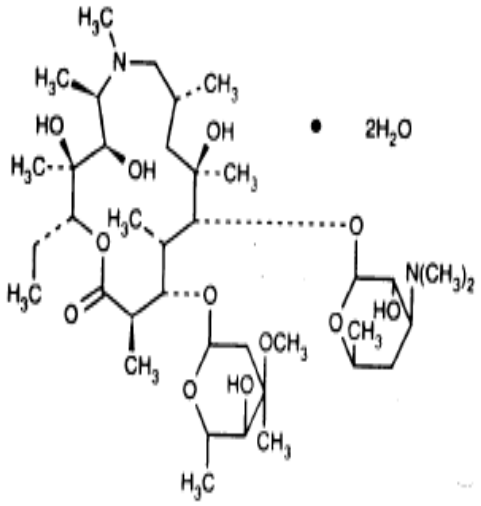

Fig. 1: Chemical structure of Azithromycin Dihydrate

MATERIALS AND METHODS

Materials

Azithromycin Dihydrate was obtained as generous gift from FDC Limited, Mumbai. Urea (Analytical grade) was purchased from Qualikems Fine Chemicals Pvt. Ltd., New Delhi. All other chemical reagents were of analytical grade.

Methods

Preparation of Physical Mixture

Accurately weighed amount of Azithromycin Dihydrate and urea (carrier) in various drug-to-carrier weight ratios were thoroughly blended in glass mortar for 5 min. The composition of various batches is shown in Table 1. The products were kept in desiccator for further study.

Preparation of Solid Dispersion

The solid dispersions of Azithromycin Dihydrate and urea (carrier) in various drug-to-carrier weight ratios were prepared by solvent evaporation method. The 100 mg of Azithromycin Dihydrate was dissolved in 20 ml of methanol in a beaker and carrier was added and mixed to dissolve at 40°C on a hot plate to get a clear solution. Then the solvent was allowed to evaporate. The process of evaporation was opted until the constant weight was obtained. Solid Dispersions prepared were crushed, pulverized and sifted through mesh number 80 and stored in desiccators.

Estimation of Azithromycin Dihydrate

Azithromycin Dihydrate was estimated at 215 nm [15] using UV

spectrophotometer (Systronics Double Beam Spectrophotometer 2202). Standard curve for the estimation was prepared in phosphate buffer pH 6.0 in concentration range of 2-30 µg/ml. In this concentration range good linearity was observed with the correlation coefficient (R^2) 0.9939. The graph obeyed the Beer-Lambert's law in the selected concentration range.

Table 1: Composition of Batches Containing Azithromycin Dihydrate and Urea

Batches for Physical Mixture	Azithromycin Dihydrate (mg)	Urea (mg)	Drug : Carrier Ratio	Batches for Solid dispersion
PM1	100	100	1:1	SD1
PM2	100	200	1:2	SD2
PM3	100	300	1:3	SD3
PM4	100	400	1:4	SD4
PM5	100	500	1:5	SD5
PM6	100	600	1:6	SD6
PM7	100	700	1:7	SD7

Characterization of Samples

Fourier Transform Infrared Spectroscopy

All prepared solid dispersions were subjected to FTIR spectroscopic studies to determine drug-carrier interaction. FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using Fourier Transform IR spectrophotometer (Perkin Elmer, RXI FTIR System). Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and resolution was 2 cm^{-1}.

Differential scanning calorimetric studies

Differential scanning calorimetry (DSC) measurements were carried out on a scanning calorimeter (DSC Q10 V9.0 Build 275, Universal V4.1D TA Instruments). The instrument was calibrated using indium as standard. Samples (5-10 mg) were placed in sealed aluminium pans and heated from 70°C to 150°C at a rate of 10°C/min under nitrogen atmosphere (60 ml/min), with empty pan as reference.

X-Ray Diffraction Studies

The powder x-ray diffraction (XRD) was performed by X'pert Pro with Spinner PW3064 using Ni-filtered, CuKα radiation, a voltage of 45 kV, and a current of 40 mA with a scintillation counter. The instrument was operated in the continuous scanning speed of 4°/min over a range of 5°C to 40°C.

Drug Content

Solid dispersions equivalent to 100 mg of Azithromycin Dihydrate were weighed accurately and dissolved in a suitable quantity of phosphate buffer pH 6.0. The solutions were filtered and drug content was determined at 215 nm by UV spectrophotometer (Systronics Double Beam Spectrophotometer 2202) after suitable dilution. The percentage

yield of each formulation was also calculated.

Saturation Solubility

To evaluate the increase in solubility of Azithromycin Dihydrate, physical mixture and solid dispersions, saturation solubility measurements were conducted. The known excess (approximately 50 mg) of Azithromycin Dihydrate was added to 100 mL of phosphate buffer (pH 6.0). Samples were rotated at 20 rpm in a water bath (37.0 ± 0.5°C) for 48 hours. The samples were then filtered, suitably diluted, and analyzed by UV spectrophotometer at 215 nm.

Dissolution Studies

The dissolution studies were performed using a US Pharmacopeia XXIV type II dissolution test apparatus. The samples equivalent to 100 mg Azithromycin Dihydrate were placed in a dissolution vessel containing 900 mL of phosphate buffer (pH 6.0) maintained at 37.0 ± 0.5°C and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration, concentration of Azithromycin Dihydrate was determined spectrophotometrically at 215 nm.

RESULT AND DISCUSSION

Fourier Transform Infrared Spectroscopy

FT-IR studies were done to detect the possible interactions between the Azithromycin Dihydrate and urea. The characteristic peaks of Azithromycin Dihydrate, urea and physical mixtures are presented in Table 2. It was revealed that there were no differences in the positions of the absorption bands, hence providing evidence for the absence of interactions in the solid state between Azithromycin Dihydrate and urea.

Table 2: FT-IR peaks of pure Azithromycin Dihydrate, urea and physical mixture of Azithromycin Dihydrate and urea.

Description	Characterization (cm^{-1})
Azithromycin Dihydrate	2973.8, 1469.3, 1050.8 and 993.6.
Urea	3335.8, 1150.6, 787.1 and 556.9.
Azithromycin Dihydrate and Urea	3335.8, 2973.8, 1469.3, 1150.6, 1050.8, 993.6, 787.1 and 556.9.

Differential Scanning Calorimetric Studies

Differential scanning calorimetry shows sharp endothermic fusion peak at 124.9°C, which is corresponding to the melting point of Azithromycin Dihydrate [Figure 2].

X-Ray Diffraction Studies

The diffraction spectra of Azithromycin Dihydrate and urea show numerous distinct peaks indicating that both are present in a highly crystalline state. The XRD pattern of solid dispersion of sample SD5 exhibits all the

characteristic diffraction peaks of urea and crystalline Azithromycin Dihydrate, but of lower intensity. This study reveals that some Azithromycin Dihydrate still exists in the crystalline state in the solid dispersion.

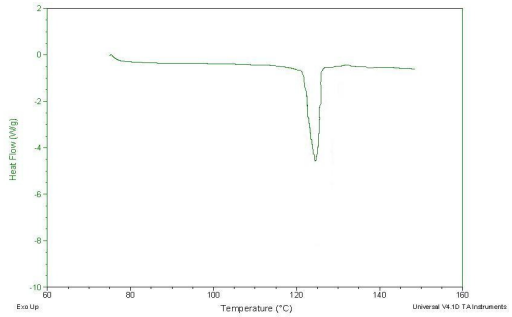

Fig. 2: Differential scanning calorimetry of Azithromycin Dihydrate.

Drug content and saturation solubility

The drug content and saturation solubility were determined and results were presented in Table 3.

Table 3: Drug content and saturation solubility of different formulations.

Product Name	Drug Content (%)*	Saturation Solubility (µg/ml)
Pure Drug	--	68.71±(1.31)
SD1	93.19±1.93	137.82±(1.28)
SD2	95.11±1.01	146.65±(2.11)
SD3	92.71±1.72	149.91±(1.61)
SD4	94.60±1.27	157.88±(1.82)
SD5	97.08±1.58	163.32±(1.34)
SD6	94.45±1.75	166.34±(1.65)
SD7	93.71±1.13	169.29±(2.02)
PM5 **	94.29±2.06	117.18±(1.21)

**Values represent mean of three individual experiments.*

***The batch having same ratio of drug: urea as compared with the best batch of solid dispersion (SD5) in term of drug content.*

Data in parenthesis represent S.D.

Dissolution Studies

The dissolution rate of pure Azithromycin Dihydrate was very poor and during 120 min a maximum about 34.22% of the drug was released. The reason for the poor dissolution of pure drug could be poor wettability and/or agglomeration or particles size. It was found that the dissolution rate of the drug increased according to increasing amount of hydrophilic carrier (urea) in physical mixture batches. This was due to the increase in solubility of drug by the presence of hydrophilic carrier surrounding the drug particles. Figure 3 shows comparative release profile of various solid dispersions of Azithromycin Dihydrate with urea, physical mixture containing 1:5 ratio of drug: urea and pure drug. From release profile it can be seen that dissolution of Azithromycin Dihydrate in solid dispersions increase with increase in urea up to 1:5 ratio of drug: urea. This increase in the dissolution rate may be due to increase in drug wettability, solubilization of drug by hydrophilic carrier and release of drug at molecular level. From the results, it was concluded that the dissolution rate of Azithromycin Dihydrate increased by preparing solid dispersion with urea.

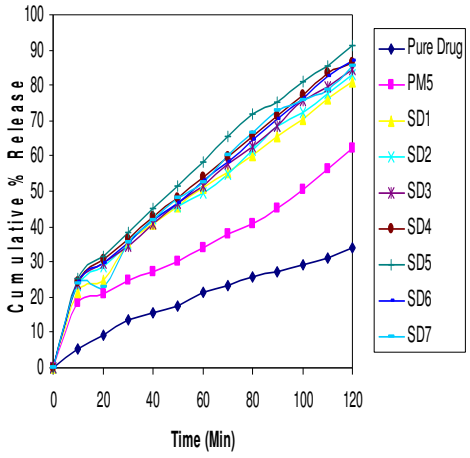

Fig. 3: Comparative *in vitro* release profiles of Azithromycin Dihydrate from solid dispersions and physical mixture containing urea.

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